FDA Policy Workshop on Osteoporosis Drug Development 04 November 2015

Question 2 - Clinical trial design elements for fracture trials including study duration, acceptability of non-inferiority designs for fracture trials, and methods for determination of a relevant non-inferiority margin

Industry Perspective

Companies Represented

- Represents the position of an industry working group of participating sponsors, participating companies were (in alphabetical order):
  - Amgen, Inc.
  - Eli Lilly and Co.
  - Merck Sharp & Dohme Corp.
  - Radius Health, Inc.
  - Sermonix Pharmaceuticals, LLC
  - Tarsa Therapeutics, Inc.

Trial Design Considerations: Drugs with Limited Duration of Use

- We propose two pathways to registration: one for agents that will be used for limited duration and one for agents that will be used chronically
- Phase III studies for agents that will be used for limited duration:
  - Proposal: if a drug is intended to be used for a limited duration, the length of phase III could be for that duration only (i.e., 12, 18, 24 months, depending on the intended treatment duration post-approval)
  - Further extension of study with switching to another drug would be choice of sponsor (and in the best interest of the patient and the sponsor)
  - First time approval of novel mechanisms of action with potential toxicities may require longer trials to understand safety, efficacy and duration of benefit

Trial Design Considerations: Drugs Used Longer Term

- For drugs shown in non-clinical studies to increase bone mass and bone strength without producing qualitative abnormalities at standard multiples of anticipated human exposure
  - A primary analysis at 2 years demonstrating fracture reduction at (at least) one site could suffice for approval

Trial Design Considerations: Drugs Used Longer Term

- Alternative scenarios include:
  - Filing with a 2 year interim analysis of a longer-term trial (e.g., 3-5 years)
    - The 2-year interim analysis may be designed to show vertebral fracture risk reduction and the final analysis designed to show hip or non-vertebral fracture risk reduction, depending on either speed of the mechanism or time to collect an adequate number of fracture events
  - Filing with a 2-year study with a longer-term (e.g., 3-5 years) conducted in parallel
    - The 2-year study may be designed to show vertebral fracture risk reduction and the longer-term study designed to show hip or non-vertebral fracture risk reduction
- Alternatively, the trial could be event-driven with a minimal exposure of 2 years for safety

Trial Design Considerations: Drugs Used Longer Term

- For drugs that increase bone mass and in non-clinical studies produce either qualitative abnormalities or smaller than anticipated increases in bone strength at standard multiples of anticipated human exposure
  - Trials that are 3-years or longer may be necessary prior to initial NDA filing
  - Extension studies may be required
  - Etidronate and fluoride would have fallen into this category based on studies in animals (2002 AdCom)
- Special considerations:
  - The Resolution of Effect data may be provided with the longer term data (as in EU) or with a separate study during review of the file

Placebo-controlled Trials

- Placebo-controlled trials provide straight-forward efficacy and safety information and have been the standard for registration of osteoporosis treatments
  - Placebo control design provides assay sensitivity and internal validity
  - Placebo control design demonstrates absolute efficacy and safety
  - Placebo control design may expose fewer subjects to test article

Placebo-controlled Trials

- The ability to perform placebo-controlled trials with appropriate safeguards in place (removal of patient with a fracture, notification of investigators and patients when a pre-established loss in BMD is documented, rigorous informed consent) varies geographically and there is heterogeneity even within a country
  - Some IRBs/countries refuse the use of placebo
  - Some IRBs/countries allow recruitment of only low-risk populations
  - Difficult to recruit high risk from a practical standpoint

- Recommendation: leave the option to choose to conduct a placebo controlled trial to the Sponsor

Trial Design Considerations: Active Controlled Trials

- Active control trials when intended to demonstrate non-inferiority to a known active agent are interpretable only when one can be sure that the active control will produce some definable effect in any given trial
- Active controlled trials have the advantages of ensuring that no patients will be exposed to placebo treatment only
- Because the safety of the investigative product can only be compared to the active comparator, that comparator must be well characterized
  - Data from phases I and II could be used for safety database or
  - Creative strategies to gather safety information include a 6 month placebo arm prior to initiation of active control, “virtual twin”, case control, adaptive designs

Trial Design Considerations: Active Controlled Trials

- Active controls are being required for reimbursement, especially in Europe
- Superiority study designs are generally accepted by all
- Issues with active control trials:
  - Cost of active comparator may be prohibitive for a smaller sponsor
  - May be prohibitively large in size depending on non-inferiority margin
  - Different doses approved in different countries
    - Propose that FDA allow Sponsor to use dosage of active control approved in each specific country
  - Labeling challenges
- Choice of active control should be proposed by Sponsor and may be difference class of drug

Trial Design Considerations: Non-inferiority Trial Designs

- A non-inferiority design can be useful for testing a drug being developed for its safety advantage or convenience to the comparator agent
- Choice of non-inferiority margin is challenging
- To select margin, suggest looking at reported treatment effect size of the comparator agent AND apply clinical judgment
- If required margin is too small, it would lead to larger trials that may not be feasible
- Benefit:risk may drive the non-inferiority margin
  - Would the acceptable results be influenced by safety results (e.g., lower bar to demonstrate efficacy if safety is greater?)
- Rigorous trial design and execution are needed to ensure validity of the study

Trial Design Considerations: Phase 2

- Currently phase 2 is required to be one year
- Phase 2 could be 6 months duration, at Sponsor's risk
  - Rationale is that most agents can select dose based on 6 month BMD data +/- bone turnover markers

Summary

- Sponsors welcome a dialogue with the Agency to discuss multiple, creative options for Phase III trial designs at varying phases of development
- Study durations
  - Phase 2 can be 6 months; Sponsor accepts risk of dose selection
  - Phase 3: trials for drugs that convey fracture benefit early AND will be used for a limited time (i.e., less than 2 years) should not be required to be of 2 year duration for demonstration of efficacy
  - Phase 3 trials for drugs for chronic use with appropriate non-clinical profiles should have the option to file for approval with 2-year data

Summary

- Sponsors should have the option to choose whether or not to conduct placebo controlled trials
- Active control trials need acceptable designs that may use different approved doses of the active control depending on local regulatory requirements; dialogue with the Agency is welcome to consider different active control doses
- The choice of non-inferiority margins involves both clinical judgment and statistical reasoning
- Benefit/risk ratio should be considered in assessment of approvability

Summary

- Sponsors would like to continue dialogue regarding label language, especially with innovative trial designs
- Sponsors are willing to help validate surrogate markers as endpoints to provide an efficient way to develop new therapies
- Sponsors would welcome a guidance for addition of descriptive long-term safety and efficacy information, if available, from extension studies into prescribing information